# PERRINE DUPONT SETTLEMENT CLAIMS OFFICE ATTN: EDGAR C. GENTLE, CLAIMS ADMINISTRATOR C/O SPELTER VOLUNTEER FIRE DEPARTMENT OFFICE

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June 23, 2017

#### VIA HAND DELIVERY

The Honorable Thomas A. Bedell Circuit Judge of Harrison County 301 West Main Street, Room 321 Clarksburg, West Virginia 26301

Re: Class Member Medical Monitoring Testing Protocols Review and Update; Our File No. 4609-1{GG-13}

Dear Judge Bedell:

I hope this letter finds the Court well.

The purpose of this Report is to present the findings and recommendations of the Medical Advisory Panel and Claims Administrator with respect to the testing protocols of the Perrine Medical Monitoring Program, regarding the need to update the current Medical Monitoring Testing Program, and to provide the rationale and details of the recommended update.

By its Order entered November 3, 2016, this Honorable Court approved the selection of a Medical Advisory Panel, as contemplated by the Court's Final Order Setting Forth the Scope and Operation of the Medical Monitoring Plan, as entered by the Court on January 18, 2011.

In its previous Order of January 18, 2011, the Court "determined that there shall be a Medical Advisory Panel to facilitate the Claims Administrator's quality control audits of the medical monitoring program, and to advise the Claims Administrator and the Court, with input from the Parties, on periodically updating medical monitoring protocols based on scientific and medical developments following the first five years of medical monitoring . . ." See Final Order Setting Forth the Scope and Operation of the Medical Monitoring Plan, page 14, paragraph 6. As such, one of the assignments of the Medical Advisory Panel, as agreed to by the Finance Committee, is the consideration of the following question:

Based upon scientific and medical developments since early 2011, do the existing medical monitoring protocols of the Perrine Medical Monitoring Program require updating?

The Panel has carefully considered this question, and the unanimous answer is "Yes."

The supporting reasoning for this decision is contained in the submissions of Doctors Pitt and Perrotta, in Exhibits A and B<sup>1</sup>, respectively. The current testing protocols are in Exhibit C, and the current tests the Panel does not recommend at this time have a line through them. The recommended updated Medical Monitoring Testing Protocols are detailed in Exhibit D, prepared by Dr. Kolar. The Panel notes that some of the monitoring may be tailored based on the participant's age and sex.

Given the scope of the recommended updates to the Medical Monitoring Testing Protocols, now testing for numerous additional maladies possibly associated with the heavy metals involved, the Panel recommends all 4,000 Class Members who originally registered for Program testing be invited again to participate in the Program.

In carrying out its duties, the Panel was provided protected access to the confidential medical testing information compiled by CTIA, in conjunction with LabCorp, for participating Class Members who consented to make the information for research. This data is maintained in a uniform database, that may be sorted and analyzed. However, the medical data obtained by Program participating Physicians sampled by the Panel on a confidential basis was not compiled in a uniform manner and is not being compiled by CTIA, so that it's accessibility for a health study or other scientific research is limited. The Panel recommends that uniform procedures and forms be developed to obtain and compile this additional participating Class Member medical testing information to facilitate its future use.

The Panel understands that the details for carrying out the findings and recommendations in this Report need to be developed in conjunction with the Settlement Administrator, the Finance Committee and CTIA, and encourages their input in responding to this Report and suggestions on how to carry it out.

Thank you for the Court's consideration.

Ed Gentle, III

Yours very truly,

Claims Administrator

<sup>&</sup>lt;sup>1</sup>Following his submission, Dr. Perrotta further clarified his position by stating that PSA is not recommended for men <u>as part of routine monitoring</u>.

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# **EXHIBIT A**

#### Overall assessment:

- a) An effective system was put in place to identify and recruit class members, employ general flow of proposed medical surveillance, maintain useful electronic records and histories, provide feedback to class members, provide secure HIPPA compatible records, interact with professional health care providers and be fiscally responsible as well as establish governance at multiple levels including medical surveillance program and its oversight.
- b) Exposure to be eligible for surveillance based on time in residence within zones of various risks of cancer based on environmental (soil) determinants of Cd, Ar and Pb. At the time, biomonitoring (blood, urine, bone, hair for Ar, Cd or Pb) considered inadequate to identify chronic low level exposures and thus may provide false sense of security. An exception being that blood Pb screening would include potential follow up via XRF for cohort of class members who were minors
- c) In the 2011 settlement, only diseases clearly associated with Ar, Cd and Pb were monitored:

Ar: skin, lung, bladder and kidney cancer

Cd: lung and kidney cancer; decreased renal function and failure

Pb: Lung, stomach and kidney CA; decreased renal function and failure; neurodevelopment in minor class member.

d) Homogeneous monitoring program for all medical monitoring group members (with exception of class members who are minors).

### Potential areas to update Perrine Medical Monitoring Program:

1) Progress in biomonitoring suggest that body burdens of Cd and Pb (less so for Arsenic) can be usefully quantified. The utility of these approaches in epidemiological studies suggests that biomonitoring can provide useful medical insight at an individual level. This should address essential personal levels of stress among the class members as well as critical elements of early detection and potential therapy. Accordingly, adding urinary analysis of Cd (and perhaps lead; with or without metal

- mobilization by chelating agents) and direct bone measurements of lead (XRF) can be added to overall surveillance.
- 2) Since 2011, a number of definitive prospective epidemiological studies including some with sufficient lag time for latent effects of chronic low level metal exposure (Strong Heart in Native Americans, HEALS in Bangladesh, Taiwan, Chile, Argentina) and prospective interventional trials (NIH TACT, NIH TACTII) have identified numerous non-cancerous endpoints not previously considered in 2011 in the context of Cd, Ar or Pb including cardiovascular, non-cancer pulmonary endpoints, metabolic and endocrine effects and neurodevelopmental, neurodegeneration and cognition.
- 3) In light of (1) and (2), modifying and contemporizing a number of laboratory and medical tests and assessments is in order. The net effect is to: a) incorporate contemporary clinical pathology and medicine; b) expand the 2011 focus on disorders that had a presumptive linearity with exposure to Ar, Cd and/or Pb to a more general view that such exposures are important contributors, as well, to common disorders; and c) have medical surveillance incorporate tenets of overall wellness.

- 1) Biomonitoring of Cd and Pb: Biomonitoring of arsenic remains beyond the scope of interrogating chronic low level exposures (due to intrinsic short half life of arsenic). Alternatively, body burdens of relevant long half life compartments of Cd (renal accumulation as reflected in urinary Cd) and Pb (bone accumulation) have been utilized in epidemiologic studies for many years and post 2011 reports (including some technologic and physiologic modifications) suggest consideration of incorporating biomonitoring of Pb and Cd (including some new technologies) in both adult and minor class members.
- a) Cadmium: Considerable use of urinary Cd levels (normalized to creatinine; either single spot or first morning void) as a biomarker of chronic low level Cd exposure (rather than a determinant of acute Cd exposure as described in an occupational setting in settlement of 2011) is now suggested as a common approach in prospective epidemiological studies (Vacchi-Suzzi et al, 2017). It has been employed in prospective study of native Americans (Garcia-Esquinas et al, 2014) including measurements of urinary Cd fifteen years after sample was procured, Canadian Health Measures Survey (Garner and Levallois, 2017), Mae Sot District of Thailand (Nishijo et al, 2014), World Trade Center-Health Program (Vacchi-Suzzi et al, 2017) and Third National Health and Nutrition Examination Survey (Adams et al, 2012). Care must be taken to account for confounding sources (tobacco products; diet) and concurrent renal disease.
- b) Lead: Although blood lead levels remain important criteria in the pathophysiological spectrum of lead intoxication (plumbism), their short half life (<30 d) and their uncertain equilibrium with larger more stable (half lives >10-30 yrs) in bone has prompted more direct quantitation of the latter. In particular, blood lead captures recent exposure as well as lead that has been mobilized from bone; lead levels in bone (tibia and patella) are an indicator of chronic cumulative exposure and are the source of lead that is mobilized to blood (Hu, Shi, Rothenberg and Schwartz, 2007). Since the 1990's, epidemiologic studies have shown that the most important standard for predicting adverse health outcomes is not recent lead exposure but rather cumulative exposure over many years with or without the additional dimension of latency (Hu H and Shih R et al, 2007). This has resulted in large number of studies utilizing XRF (X-ray fluorescence) that suggest that: a) bone lead measurements may be useful indicator of prior exposure to lead; and b) bone lead stores, themselves, are a risk factor for future toxicity (Hu et al, 1995; Hu 1998). Indeed XRF was proposed as a followup to detection of potentially elevated levels of blood lead in the cohort of minors in 2011 settlement. The physical principles, limitations and subtleties of various Xray fluorescence techniques is the subject of considerable longstanding interest

(Todd and Chettle, 1994). The feasibility of a portable x-ray tube based KXRF system to measure lead in bone has been proposed by Weisskopf and colleagues (Nie LH et al, 2011) and a device manufactured by Thermo Fisher was employed in exposure study in children in China (Specht et al, 2016) and recently refined further by these authors (Specht et al, 2017). A number of these efforts include comparison of bone lead with blood lead and conclude (Specht et al, 2016) that bone Pb, at least in children, may be a better marker for determination of chelation efficiency.

c) Future determinations of Cd and Pb in class members who are minors; tooth exposome. The most recent efforts in measuring body burden of metals in children is the use of laser ablation inductively coupled plasma mass spectrometry (LA-ICP) in shed deciduous teeth (Modabbernia eet al, 2016). The technology facilitates reconstructing environmental exposures, including Cd and Pb, longitudinally from second trimester through first year of life and was most recently reported in a new study on fetal and postnatal metal dysregulation and autism in a study on twins in Sweden (Arora M et al, 2017).

### 2) Potential non-cancer endpoints to add to medical surveillance:

a) Cardiovascular disease: As noted by Cosselman et al (2015), arsenic, cadmium and lead advance disease and mortality via augmentation or initiation of pathophysiological processes associated with cardiovascular disease (blood pressure control, carbohydrate and lipid metabolism, vascular function and atherogenesis). As such metal exposure adds significantly to the risk of cardiovascular disease from traditional factors (smoking, diabetes, dyslipidemia, etc). Chronic exposure to arsenic (Naujokas MF et al, 2013) is now associated with increases in ischemic heart disease and (systolic) hypertension (Chen Y et al, 2011: Gong and OBryant 2012; Abhyankar et al, 2012) and prolongation of Q-T interval (Wu et al, 2014). Epidemiological studies have also associated cadmium levels in blood or urine with the incidence of and mortality from cardiovascular disease, stroke, coronary heart disease, heart failure, carotid plaque development, peripheral arterial disease and renal dysfunction (Cosselman et al, 2015; Tellez-Plaza et al, 2012; Tellez-Plaza et al, 2013; Fagerberg et al, 2015; Myong et al, 2014; Chung et al, 2014; Franceschini N et al, 2017). Lead has been long known to be associated with adverse cardiovascular outcomes (Navas-Acien et al, 2007; Kim et al, 2015)

- b) **Diabetes:** Although an association has long been suspected between **arsenic** exposure and type 2 diabetes (Maull et al, 2012), improved exposure and outcome metrics (Beck, Styblo and Sethupathy, 2017) have secured this association (Kuo C-C et al, 2015).
- c) Pulmonary (non-cancer): Although Ar and Cd have well documented associations with lung cancer (as outlined in settlement in 2011), recent epidemiological studies have associated exposure to heavy metals and non-cancer pulmonary endpoints including: a) blood levels of Cd and Pb and obstructive lung function in Korean (Leem At et al 2015) and US (Rokaida and Agarwal, 2013) National Health Surveys; b) urinary Cd and asthma in Wuhan China (Huang et al, 2016); c) urinary arsenic and impaired lung function (decrements in FEV1 and FVC) in Health Effects of Arsenic Longitudinal study (HEALS) in Bangladesh (Parvez et al, 2013); and d) arsenic and respiratory symptoms in children (Smith AH et al, 2013).
- d) *Nervous system:* The impact of **lead** on neurodevelopment and behavior is well established and is a foundation in environmental and public health. As such, it was incorporated in the 2011 settlement for assessment and follow-up in the class members that are minors. Recent evidence has expanded the disease and syndrome endpoints of concern with lead including autism spectrum disorder (Arora et al, 2017) and early life exposure to lead and adult schizophrenia (Modabbernia et al, 2016). A critical review of cadmium toxicity literature suggests there is little support for **Cd** affecting cognition or attention deficit hyperactivity (Sanders, Henn and Wright, 2015). In contrast, **arsenic** may impair cognitive function in pre-school girls, but not boys (Hamadani et al, 2011) and motor function (Parvez et al, 2011).
- e) **Bone and mineral metabolism:** Bone fragility is well known consequence of **cadmium** and **lead**. As such, it was mentioned in the 2011 settlement although precise medical and laboratory assessment was not outlined.
- f) *Kidney:* As with bone changes, both **cadmium** and **lead** are known to cause acute tubular and chronic glomerular changes. These assessments were described in 2011 settlement and refinements are now outlined for future surveillance of kidney function.

#### 3) Other Considerations

a) Metal mixtures: As noted above, an essential challenge in the design of medical surveillance is useful quantitative assessment of exposure. The likelihood that an individual may have been exposed to all three metals or combinations and permutations of exposure to Cd, Ar and Pb, greatly exacerbates potential concerns. Attempts to approach this are appearing in literature (Sanders et al, 2015; Bizon et al, 2016; Yang WY et al, 2017). The likelihood of incorporating developing understanding for this important issue in the context of medical surveillance requires confirmatory and new studies in the future. As such, the assumption that all individuals may have been exposed to all three metals appears pragmatic and identifying potential adverse outcomes as an accumulation of potential effects of each single metal appears to be the only practical way to address concerns in 2017.

#### b) Chelation:

- i) one time provocative Cd (or lead) mobilization to urine for exposure: The potential to enhance the sensitivity of urinary measures of Cd or Pb by a one time chelation approach (2,3 dimercaprol, dimercaptosuccinic acid or disodium EDTA (Waters et al, 2001; Kalia and Flora, 2005; Hoet et al, 2006) might be considered.
- ii) interventional TACT and TACT II. The biomedical fundamental principles of medical surveillance comprise value of early detection and prevention for potential therapies. In this regard, recent outcomes of NIH sponsored Trial to Assess Chelation Therapy; TACT) has significant relevance for the health outcomes of class members. In a prospective, large, randomized placebo control study, EDTA chelation therapy significantly reduced cardiac events in stable post-myocardial infarction patients (Lamas et al, 2013). This therapeutic benefit was exacerbated in patients with diabetes melliltus and prior myocardial infarction (Escolar et al, 2013). This unexpected outcome has prompted a second TACT trial for replicative purposes focused on the later cohort and also suggested the mechanism underlying efficacy of EDTA chelation may have been removal of toxic metal stores in the body (Lamas et al, 2016).

c) Stratification (susceptibilities) – gender, age, genetics, smoking, obesity, confounding disease, etc The 2011 settlement provides for a homogenous medical surveillance plan (with the exception of the class members that are minors). Although this is of significant pragmatic value, it is apparent that the health effects of individual and collective metals may be specific as a function of gender, age, genetics, confounding disease, lifestyle (drugs, exercise, diet).

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# **EXHIBIT B**

### Summary of Recommendations for Changes to Medical Monitoring Program Peter Perrotta 06/06/2017

#### Additions to the Program

Smoking cessation program: This is suggested as the risks of heavy metal exposure are likely more than cumulative when combined with other risk factors like smoking.

Add education in self-skin exam to regular skin checks every 2 years: A simple pamphlet showing how to perform a self-skin exam would complement the current screening every 2 years.

Complete Blood Count w/differential to assess long-term bone marrow effects.

Add hemoglobin A1c for diagnosis and monitoring of serum glucose for diabetes mellitus (DM). The fasting blood glucose level can be maintained.

Serum uric acid testing is indicated. Pb & Cd exposures causing renal damage have been associated with increased uric acid and gout.

Regular cognitive, neurological, and depression screenings: This is part of the monitoring, however, this could be more standardized and documented better.

Substitute Fecal Immunochemical Test (FIT) for the Fecal Occult Blood Test (FOBT)

- FIT removes the pre-collection dietary restrictions necessary for accurate test results. This alone decreases the risk of false-negative results.
- FIT allows a slightly larger sampling of specimen in some cases and better stability. This
  provides better sensitivity than the FOBT test.
- Colonoscopy is indicated if FIT testing is positive

Hepatic (liver) function testing (total protein, albumin, total bilirubin, alkaline phosphatase (ALP), LDH, AST/ALT) is recommended with the associated caveats:

- DM can cause mild to moderate changes in liver function tests.
- Metal toxicity tends to cause cirrhosis with an initial hepatitis pattern, with low enzyme markers in end-stage cirrhosis.
- Arsenic can inhibit osteoblastic activity to reduce bone turnover. This reduces bone ALP,
   which is a prominent component of circulating ALP.

Although creatinine clearance is best for assessing renal damage, we recommend serum creatinine with an estimated glomerular filtration rate (eGFR) as acceptable for screening & monitoring. Also, add a random urine microalbumin/creatinine ratio and a random urine protein for monitoring. Note:

 If renal disease is diagnosed, follow-up studies to consider include measures of serum vs urine calcium and phosphorus, which would be more useful (and less expensive) as direct indicators of damage rather than indirect ones (eg, beta-2-microglobulin in urine) Urinalysis: We recommend continuing routine urinalysis with microscopic, recognizing the limited utility of this testing. Serum-based assessments and urine microalbumin & protein are better screens for renal damage. Metals don't make crystals, and any casts found on urinalysis would not be specific to heavy metal exposure.

One time urine measurements for all 3 metals is recommended, recognizing that this testing is most useful for As & Cd exposure.

Urine pregnancy/hCG screening prior to any imaging in females of childbearing age. This is standard procedure.

Periodic imaging, long bones: This is a preliminary suggestion and should be limited to children.

- There are different influences of the mentioned metals on bone function.
- Cadmium and Arsenic exposures tend to associate with osteonecrosis, osteomalacia, and osteoporosis.
- X-ray fluorescence of long bones is suggested in children for assessment of growth retardation in exposed children per CDC but no recommendation was made for utility in adults.
- While this test could provide a burden assessment, there are conflicting data in PubMed about whether Cd & As co-exposures interfere with the Pb burden assessment. This may be relevant in this case as co-exposures are possible and may complicate this means of monitoring.

Ultrasound of liver rather than CT if cirrhosis is not already present

- Could be a useful, inexpensive, and non-invasive/low-risk means of assessment if CT is not really deemed necessary by other assessments.
- CT could then be performed only if ultrasound demonstrates changes, if biopsy isn't yet favored to diagnose and stage the cirrhosis.

We also recommend that a data collection form/template be provided to participating providers so that data collection can be more standardized.

Consider bone densitometry for woman.

**Testing that can be stopped or should not be considered:** Some testing has questionable clinical utility and/or is now discouraged by CDC (<a href="https://www.atsdr.cdc.gov/">https://www.atsdr.cdc.gov/</a>):

- Blood-based metals measurements: Metals have short circulation half-lives, making them
  more appropriate for acute exposure than chronic testing. Urine testing is generally more
  useful for chronic burden & clearance assessment.
- Zinc & free RBC protoporphyrin: These tests are now considered obsolete in most applications, including toxic metal exposures.
- "Assay of beta-2 protein in urine": This is an indirect assessment of tubular damage. CDC sources note that both the glomerulus and tubule are damaged in these metal exposures.
   There is more evidence that urine testing for other analytes (eg, glucose, calcium, phosphate) might be more useful, although we do not recommend this at this time.
- Sedimentation rate: Now considered obsolete in all but an isolated few clinical applications, and only when considered with other clinical and lab-based data. This test lacks specificity.
- PSA is not recommended for men for this monitoring
- Vitamin D testing is not recommended

# **EXHIBIT C**

			¥
8420 84520 84520 85025 86652 88304 88305	74178 74177 74177 74178 96118 96109 81005 8204 82265 82274 82265 82247	43239 71250 71260 74150 74160	32096 32097 32098
HAGGYTE PROTOPORPHYRIN  OCUNT (OBC) WITH DIFFERENTIAL  VITE (ESR)  VATHOLOGIST  PATHOLOGY, GROSS & MICROSCOPIC EXAMINATION	WITH CONTRAST PELVIS WITH CONTRAST PELVIS WITH CONTRAST PELVIS WITH CONTRAST PELVIS WITH CONTRAST IN ONE OR BOTH BODY REGIONS FOLLOWED BY CONTRAST MATERIALS IN ONE OR BOTH BODY REGIONS PELVIS WIO CONTRAST IN ONE OR BOTH BODY REGIONS FOLLOWED BY CONTRAST MATERIALS IN ONE OR BOTH BODY REGIONS PERCHAPHYS PERCHAPHYS PROTEIN WITH MICROSCOPIC EXAMINATION PARCHEL WITH MICROSCOPIC EXAMINATION PARCHEL WITH WICHOSCOPIC EXAMINATION PARCHEL WITH WICHOSCOPIC EXAMINATION PARCHEL WITH WITH WITH WITH WITH WITH WITH WITH	COPY, BIOPSY  YE  CONTRAST  N WITH CONTRAST	BIOPSY THROUGH CHEST WALL BIOPSY LING, PERCUTANEOUS NEEDLE BRONCHOSCOPY
Age 15 and over All ages	Age 35 and over Age 15 and over	All ages All ages All ages Age 35 and over	Aug All ages
Both Both Both Both Both Both Both	Both Both Both Both Both Both Both Both	Both Both	Sex

### **EXHIBIT D**

		7	No	Stomach Cancer	GI		43
		Tobacco hx/Cessation namphlet	T				
		Lipid Panel					42
		Exam		CVD			41
	Yes .	CT Scan Lungs		HTN			40
	Yes	Audiogram		Lung Cancer	Resp		39
		rxaiii		Hearing Loss			38
				Tooth Loss	Head/Neck	Lead	_
1945-1965	1.	AIH	No				_
Born between	B	Hep C Screen	No				35
		CBC/ Diff	No	in color			
		Uric Acid		mmunosupression	All/Immun		34
and over	<u>a</u>	עפאמטרמוו		SOL+			33
Females aged 65		Devascan	No	Osteoporosis			32
	Yes	X-ray	No	sone Fragility	VIV		F
	Yes	Urine Calcium	No	:	NAC .		2 2
		U/A	Yes	Kidney Stones			3 5
	Yes		No	Prostate Bioposy Follow-Up			20
	Yes	PSA		Prostate Cancer			36
		A/N	Yes	Renal Cell Cancer			77
		GFR					3 2
		Cr		Kidney Damage/failure	G		2 5
		PFTs		COPU/ emphysema			24
	Yps	CT Scan Lungs	Yes	Lung Cancer	Resp	Cadmium	7 6
					,	Color	_
		Urine Micro albumin/creatinine ratio	No				27 5
		Hgb A1c	No				3 5
		Glucose	No	DM	Endo		0 6
	Yes	Carotid U/S					2 5
	Yes	CT Scan Brain		CVA			17
	Yes	EMG		Peripheral Neuropathy	Neuro		7 5
		Cr			No		5 5
		U/A		Renal Cell Cancer			7 5
		Urine Cytology					7 7
		U/A	Yes	Bladder Cancer	60		3 F
		LFTs		Elevated bilirubin/alkaline phosphatase	)		1 5
	Yes	U/S	No	Hepatomegaly			م ا
	Ypc	U/S	No	Hepatic angiosarcoma	GI		×
		EKG	No	prolonged QTc			1
מינט נטטמניני		Tobacco hx/Cessation pamphlet	No				10
Men 65-75 and	Yes	Abdominal Aortic Ultrasound (U/S)	No				2 0
		Lipid Panel	200	CVD/CAD	(		_
	Yes	PFTs		Decreased Lung Function	5		4
	Yes	CT Scan Lungs	Yes	Possonal in Franti-	7000		w
(None where none shown)	By Referral?	nagilostic lest	Program Protocols?		Resn	Arsenic	2
Qualifications	,	Disposition Total	Currently in Medical Monitoring	Disease By System	Body System	Element	
	F	ш	D	C	8	Δ	